UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/939,476	08/23/2001	Evan Y. Snyder	701039-051500-C	5389

7590 10/21/2003

NIXON PEABODY LLP
101 Federal Street
Boston, MA 02110

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/939,476	Applicant(s) SNYDER ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636	

-- Th MAILING DATE of this communication appears on th cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The application has been transferred to Examiner Quang Nguyen, Ph.D., in the GAU 1636.

Applicants' amendment filed on 7/30/03 in Paper No. 12 has been entered.

Amended claims 16-22 are pending in the present application, and they are examined on the merits herein. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 16-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the previous Office Action in Paper No. 10 (pages 4-7).

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 7/30/03 in Paper No. 12 (pages 6-10) have been fully considered, but they are respectfully found to be unpersuasive.

(1) Applicants argue that at least 3 out of about 23 ongoing gene therapy clinical trials in the US are reported already on Phase III stage, and that in June 16, 2003, FDA lifted its hold on the Enzo Biochem Inc. clinical trial relating to HIV gene therapy. Thus, these developments argue against a generalized contentions of complete lack of success of gene therapy trials.

It is unclear that any of gene therapy clinical trials in phase III stage is related to the nature of the presently claimed invention (e.g., the utilization of genetically modified mammalian neural stem cells as vehicles to deliver any protein product or any recombinant viral vector to treat any tumor (both neural and non-neuronal tumors) in a mammal by any route of administration). However, Applicants' argument does support a contention that the attainment of therapeutic effects (at least for clinical trials in phase III) via gene therapy was highly unpredictable (only three clinical trials in phase III out of hundreds of clinical trials being conducted since 1990). The unpredictability for the attainment of therapeutic effects via gene therapy is clearly evident by the reviews of Paulu et al., Verma et al. and Park et al. To further support the Examiner's position, even in light of the results presented by the present application in the form of the article of Aboody et al. (PNAS 97:12846-12851, 2000), Noble (PNAS 97:12393-12395, 2000) states "As discussed, **the problems that remain to be resolved in obtaining benefit**

from this novel therapeutic approach are formidable ones....A number of such treatments have been proposed, including vaccination, gene therapy, pharmacological blockade of specific receptors involved in glioma growth, and the application of angiogenesis inhibitors. All of these various treatments have been applied successfully in rodent models, but **it is not yet clear whether any will prove of clinical value**. As, thus far, **none of the treatments of brain tumors that have been successful in preclinical models have worked in human patients, the need for continued research in this arena remains as great as it has ever been**" (page 12394, col. 3, last paragraph continues to page 12395). Some of the problems or concerns raised by Noble include: (a) whether the therapeutic agent produced by the transplanted neural stem cells would cause injury to normal brain cells, (b) how to engineer the stem cells to cease producing the therapeutic protein, (c) the use of nonautologous stem cells will trigger an adverse host immune response (page 12394, col. 2, bottom of first paragraph). Moreover in 2002, Park et al. (Gene therapy 9:613-624, 2002) reference which includes two of the inventors as authors note that "the field of NSC biology is at a very early state of development", and that "**many of our suggestions are highly speculative**" and that "**many important questions need to be addressed experimentally before using such cells in clinical applications**" (page 622, second column). Furthermore, in light of the overall state of the art at the effective filing date of the present application (10/07/1998), it would be reasonable to assume that the demonstration that immortalized mouse neural progenitor C17.2 cells expressing β-

galactosidase migrate throughout and beyond invading tumor mass in a nude mouse model is not correlated to any therapeutic effects contemplated by Applicants.

(2) With respect to the issue of a sustained transgene expression *in vivo*, Applicants argue that treatment of tumors is not intended to last a long time unlike in the treatment of inherited diseases such as cystic fibrosis, haemophilias and X-SCID. Applicants further argue that the cited references of Palu et al., Verma et al., and Park et al. are all related to clinical and therapeutic efficacy, which is not the standard that is to be used in the PTO.

Although a sustained or long-term transgene expression *in vivo* is not required for the treatment of tumors, an effective expression level of a transgene (e.g., cytokines, receptors for trophins, differentiating agents, prodrug activating enzymes) must be produced to yield the desired therapeutic effects contemplated by Applicants. The attainment of an effective transgene expression *in vivo* to yield any therapeutic effect was highly unpredictable as evidenced by the state of the prior arts at the effective filing date of the present application.

Examiner notes that that presently claimed invention is drawn to a method of treating a tumor in a mammal (human included), which is clearly drawn to the attainment of therapeutic effects in a tumor treatment.

(3) With respect to the issue on the unpredictability of an animal model, Applicants argue that the rat glioma model (D74) which applicants describe in the

present application is one of the best glioma animal models, and that it is well known in the art that the D74 rat glioma has been refractory to a variety of therapeutic modalities and its invasive pattern of growth and uniform lethality makes it a particular attractive model to test new therapeutic modalities.

As noted previously, even in light of the results presented by the present application in the form of the article of Aboody et al. (PNAS 97:12846-12851, 2000), Noble (PNAS 97:12393-12395, 2000) states "As discussed, **the problems that remain to be resolved in obtaining benefit from this novel therapeutic approach are formidable ones**....A number of such treatments have been proposed, including vaccination, gene therapy, pharmacological blockade of specific receptors involved in glioma growth, and the application of angiogenesis inhibitors. **All of these various treatments have been applied successfully in rodent models, but it is not yet clear whether any will prove of clinical value**. As, thus far, **none of the treatments of brain tumors that have been successful in preclinical models have worked in human patients, the need for continued research in this arena remains as great as it has ever been**" (page 12394, col. 3, last paragraph continues to page 12395). Moreover, on the same issue Noble (Nature Medicine 6:369-370, 2000; Cited previously) states that "Even if disseminated tumor models were more widely used, it is obvious that **the ability of a treatment to be effective across the distance of a mouse or rat brain provides little or no predictability of its efficacy across the much greater distances in the human CNS**", and that **the tumors used in pre-**

clinical trials consistently fail to model the extraordinary genetic variability of a malignant human tumor (page 370, col. 1, bottom of second paragraph).

(4) Applicants further ague that the manuscript authored by the inventors submitted in Appendix I provides evidence that the tumor treatment of the present invention is indeed successful. The findings set forth in the manuscript support the use of neural stem cells as an effective delivery vehicle to target and disseminate therapeutic agents to invasive tumors of neural and non-neural origin, both within and outside the brain.

Examiner would also like to note that the results observed in the post-filing manuscript are irrelevant because the method that is described in the manuscript involves the step of intravascular delivery of the neural stem cells into adult nude mice implanted with neural and/or non-neural tumor cells within or outside the brain, and that this step has not been taught or supported by the present application. Applicants are invited to point out the specific page number, specific line numbers in the present disclosure that provides written support for such a step.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

GERRY LEFFERS
PRIMARY EXAMINER